# Network Meta-Analysis: Importance of Appropriate Trial Selection

To the Editor—Network meta-analysis (NMA) is a technique that is increasingly employed in health technology appraisal to generate comparative efficacy and safety data for treatments not compared directly in randomized controlled trials. The National Institute for Health and Clinical Excellence (NICE) has recommended its use when direct comparator trials are unavailable [1]. As discussed in the article by Hawkins et al. [2], it is important to include all relevant and informative data in an NMA. Inappropriate study selection can have a huge impact on results and lead to erroneous conclusions. This would appear to be the case in the selection of studies for the extended NMA presented in this article.

The objective of the clinical example was to assess overall survival with erlotinib compared with docetaxel in the second-line treatment of stage III/IV non–small-cell lung cancer (NSCLC). When presented with the extended NMA as part of the single technology appraisal of erlotinib in the treatment of NSCLC, the NICE appraisal committee raised concerns about the lack of comparability of patient populations for some of the studies included within the network [3]. For example, the Iressa Survival Evaluation in Lung Cancer (ISEL) trial [4] comparing gefitinib versus placebo, the largest trial in the extended network and the main driver of the different conclusions between the limited and the extended NMAs, included a very high proportion of chemotherapy refractory patients (90%). The refractory nature of the ISEL population may account for the failure of this study to show superiority versus placebo in terms of overall survival, although the BR21 trial of erlotinib versus placebo succeeded in a less refractory population. Hence, inclusion of the ISEL trial may violate the exchangeability assumption in the NMA. In addition, as presented in Table 2 in the Hawkins et al. article, ISEL and BR21 [5] included a substantial proportion of patients that had received more than one previous chemotherapy (50% in both studies). This third-line setting is not consistent with the second-line objective of the analysis.

The consistency of the study populations and the number of previous treatments received are key features that need to be assessed when making an assumption of exchangeability of data within an NMA. Based on the study population, it could be argued that the ISEL trial should be excluded from the NMA. If it is to be included, however, data on second-line only patients should be used from both this and the BR21 study. These data, as well as the relevant second-line data from the other trials included in the extended NMA, are presented in Table 1.

Based on the second-line data, an NMA, using docetaxel as a baseline for comparison, produces the results presented in Table 2. All four active treatments have similar survival to each other, and best supportive care has a shorter survival. The very different conclusions from this analysis, the limited NMA, and the extended NMA presented by Hawkins et al. illustrate the high sensitivity of the modeling results to the selection of studies included.

We welcome the methodological recommendations for NMA presented by Hawkins et al. that have been highlighted by previous researchers [12,13]. In implementing this NMA, however, we stress the importance of appropriate study selection: studies included should be relevant to the objective of the analysis and include comparable patient populations such that the exchangeability assumption is met. This is particularly important when only a few studies provide information on each of the treatments included in the NMA, as in this example (five comparators from six studies), as inclusion of inappropriate data can have undue weight on the results.

NMA can be a useful tool when direct comparative data are not available, but randomized controlled trials remain the gold standard for comparing the efficacy and safety of two treatments.—Steven J. Edwards, DPhil, and John Borrill, MSc, AstraZeneca UK Ltd, Luton, Bedfordshire, UK.

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**Table 2** Hazard ratios (HRs) for overall survival from the network meta-analysis using docetaxel as the baseline treatment (HR < 1 is better than docetaxel; HR > 1 is worse than docetaxel)

| | | 95% credible interval | |
|---|---|---|---|
| Treatment | Mean | Lower | Upper |
| Docetaxel | 1.00 | Baseline | Baseline |
| BSC | 1.32 | 1.07 | 1.61 |
| Gefitinib | 0.98 | 0.87 | 1.10 |
| Erlotinib | 1.02 | 0.69 | 1.44 |
| Pemetrexed | 1.00 | 0.82 | 1.20 |

BSC, best supportive care alone or with placebo.

**Table 1** Hazard ratios (HRs) for overall survival for randomized controlled trials informing the network meta-analysis for second-line treatments for stage III/IV non-small cell lung cancer (HR < 1 treatment is better than comparator; HR > 1 treatment is worse than comparator)

| Trial | Treatment | Comparator | HR (95% confidence interval) | Log HR (SE) |
|---|---|---|---|---|
| BR21 [5,6] | Erlotinib | BSC | 0.76 (0.60–1.10) | –0.27 (0.15) |
| JMEI [7] | Pemetrexed | Docetaxel | 0.99 (0.82–1.20) | –0.01 (0.10) |
| TAX 317 [8] | Docetaxel | BSC | 0.48 ($P = 0.004$) | –0.73 (0.25) |
| ISEL [4,9] | Gefitinib | BSC | 0.80 (0.66–0.97) | –0.22 (0.10) |
| INTEREST [9,10] | Gefitinib | Docetaxel | 0.96 (0.85–1.08) | –0.04 (0.06) |
| SIGN [11] | Gefitinib | Docetaxel | 0.97 (0.61–1.52) | –0.03 (0.23) |

BSC, best supportive care alone or with placebo; SE, standard error.

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## References


1 National Institute for Health and Clinical Excellence (NICE). Guide to the methods of technology appraisal. 2008. Available from: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf [Accessed October 26, 2009].

2 Hawkins N, Scott DA, Woods BS, Thatcher N. No study left behind: a network meta-analysis in non-small-cell lung cancer demonstrating the importance of considering all relevant data. Value Health 2009;12:996–1003.

3 National Institute for Health and Clinical Excellence (NICE). NICE technology appraisal guidance 162: erlotinib for the treatment of non-small-cell lung cancer. Available from: http://www.nice.org.uk/nicemedia/pdf/TA162Guidance.pdf [Accessed October 26, 2009].

4 Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 2005;366:1527–37.

5 Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;14:123–32.

6 Roche. Tarceva® (elotinib) NICE STA Submission. Available from: http://www.nice.org.uk/nicemedia/pdf/Lungcancer_erlotinib_manusub.pdf [Accessed November 12, 2009].

7 Hanna N, Shepherd FA, Fossell FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589–97.

8 Shepherd F, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095–103.

9 AstraZeneca UK Ltd. Data on file IRE/031/Nov 09 [Available on request from AstraZeneca].

10 Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet 2008;22:1809–18.

11 Cufer T, Vrdolijak E, Gaafar R, et al. Phase II, open-label, randomised study (SIGN) of single-agents gefitinib (IRESSA) or docetaxel as second-line therapy in patients with advanced (stage IIIb or IV) non-small-cell lung cancer. Anticancer Drugs 2006;17:401–9.

12 Caldwell DM, Gibb DM, Ades AE. Validity of indirect comparisons in meta-analysis. Lancet 2007;369:270.

13 Salantini G, Higgins JPT, Ades AE, Ioannidis JPA. Evaluation of networks of randomized trials. Stat Methods Med Res 2008;17:279–301.